Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

*ОРИГИНАЛЬНАЯ СТАТЬЯ*

*DOI: 10.19163/2307-9266-2021-9-3-195-204*



# EFFECT OF SOLID DISPERSIONS ON THE SOLUBILITY OF METRONIDAZOLE

**I.I. Krasnyuk (Jr.)[1], S.R. Naryshkin[1], I.I. Krasnyuk[1], A.V. Belyatskaya[1], O.I. Stepanova[1], I.S. Bobrov[1], V.G. Yankova[1], J.V. Rau[1,2], A.N. Vorobiev[3]**

[1] Sechenov First Moscow State Medical University
Bldg. 2, 8, Trubetskaya St., Moscow, Russia, 119991
[2] Istituto di Struttura della Materia, Consiglio Nazionale delle Ricerche (ISM-CNR)
Via del Fosso del Cavaliere, 100-00133 Rome, Italy.
[3] Peoples' Friendship University of Russia
6, Miklukho-Maclay St., Moscow, Russia, 117198

E-mail: krasnyuk.79@mail.ru

Received 5 March 2021 Accepted 15 June 2021

**The aim** of the work is to study the effect of solid dispersions using polyethylene glycols of various molecular weights on the solubility of metronidazole in water. Metronidazole is an antimicrobial and antiprotozoal drug. Its low solubility in water limits the use of metronidazole, causing technological difficulties and reducing its bioavailability. The solubility and release of the active substance from dosage forms can be increased using the solid dispersion methods. Solid dispersions are bi- or multi-component systems consisting of an active substance and a carrier (a highly dispersed solid phase of the active substance or molecular-dispersed solid solutions) with a partial formation of complexes of variable compositions with the carrier material.
**Materials and methods.** The substance of metronidazole used in the experiment, was manufactured by Hubei Hongyuan Pharmaceutical Technology Co., Ltd. (China). To obtain solid dispersions, polyethylene glycols of various molar masses – 1500, 2000 and 3000 g/mol – were used. The solid dispersions were prepared by "the solvent removal method": metronidazole and the polymer were dissolved in a minimum volume of 96% ethyl alcohol (puriss. p.a./analytical grade) at 65±2°C, and then the solvent was evaporated under vacuum to the constant weight. A vacuum pump and a water bath were used at the temperature of 40±2°C. The dissolution of the samples was studied using a magnetic stirrer with heating, and a thermostatting device. The concentration of metronidazole was determined on a spectrophotometer using quartz cuvettes at the wavelength of 318±2 nm. To filter the solutions, syringe nozzles were used, the pores were 0.45 μm, the filter was nylon. Microcrystalloscopy was performed using a microscope with a digital camera. The optical properties of the solutions were investigated using a quartz cuvette and a mirror camera (the image exposure – 20 sec).
**Results.** Obtaining solid dispersions increases the completeness and rate of the metronidazole dissolution. The solubility of metronidazole from solid dispersions increases by 14–17% in comparison with the original substance. The complex of physical-chemical methods of the analysis, including UV spectrophotometry, microcrystalloscopy and the study of the optical properties of the obtained solutions, makes it possible to suggest the following. The increase in the solubility of metronidazole from solid dispersions is explained by the loss of crystallinity and the formation of a solid solution of the active substance and the solubilizing effect of the polymer with the formation of colloidal solutions of metronidazole at subsequent dissolution of the solid dispersion in water.
**Conclusion.** The preparation of solid dispersions with polyethylene glycols improves the dissolution of metronidazole in water. The results obtained are planned to be used in the development of rapidly dissolving solid dosage forms of metronidazole with an accelerated release and an increased bioavailability.
**Keywords:** solid dispersion; solubility; metronidazole; polyethylene glycol
**Abbreviations:** SD – solid dispersion; PEG – polyethylene glycol; R&D – research & development

**For citation:** I.I. Krasnyuk (Jr.), S.R. Naryshkin, I.I. Krasnyuk, A.V. Belyatskaya, O.I. Stepanova, I.S. Bobrov, V.G. Yankova, J.V. Rau, A.N. Vorobiev. Effect of solid dispersions on the solubility of metronidazole. *Pharmacy & Pharmacology.* 2021;9(3):195-204. **DOI:** 10.19163/2307-9266-2021-9-3-195-204



**Для цитирования:** И.И. Краснюк (мл.), С.Р. Нарышкин, И.И. Краснюк, А.В. Беляцкая, О.И. Степанова, И.С. Бобров, В.Г. Янкова, Д.В.Рау, А.Н. Воробьев. Влияние твёрдых дисперсий на растворимость метронидазола. *Фармация и фармакология.* 2021;9(3):195-204. **DOI:** 10.19163/2307-9266-2021-9-3-195-204

*RESEARCH ARTICLE*

*ISSN 2307-9266 e-ISSN 2413-2241*

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

# ВЛИЯНИЕ ТВЁРДЫХ ДИСПЕРСИЙ НА РАСТВОРИМОСТЬ МЕТРОНИДАЗОЛА

**И.И. Краснюк (мл.)[1], С.Р. Нарышкин[1], И.И. Краснюк[1], А.В. Беляцкая[1], О.И. Степанова[1], И.С. Бобров[1], В.Г. Янкова[1], Д.В.Рау[1,2], А.Н. Воробьев[3]**

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет)
119991, Россия, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Институт структуры вещества Национального исследовательского совета (ISM-CNR)
Виа дель Фосссо дель Кавальере, 100-00133, Рим, Италия
[3] Федеральное государственное автономное образовательное учреждение высшего образования «Российский университет дружбы народов»
117198, Россия, г. Москва, ул. Миклухо-Маклая, д. 6.

E-mail: krasnyuk.79@mail.ru

Получено 05.03.2021 Принята к печати 15.06.2021

**Цель.** В работе изучено влияние твёрдых дисперсий с применением полиэтиленгликолей различных молекулярных масс на растворимость метронидазола в воде. Метронидазол – противомикробное и противопротозойное лекарственное средство. Малая растворимость в воде ограничивает применение метронидазола, обуславливая технологические трудности и снижая биодоступность. Повысить растворимость и высвобождение действующего вещества из лекарственных форм можно с помощью метода твёрдых дисперсий. Твердые дисперсии – это би- или многокомпонентные системы, состоящие из действующего вещества и носителя (высокодиспергированная твёрдая фаза действующего вещества или молекулярно-дисперсные твёрдые растворы) с частичным образованием комплексов переменного состава с материалом носителя.

**Материалы и методы.** В работе использовали субстанцию метронидазола производства. Для получения твёрдых дисперсий применяли полиэтиленгликоли различных молярных масс: 1500, 2000 и 3000 г/моль. Твердые дисперсии готовили методом «удаления растворителя»: метронидазол и полимер растворяли в минимальном объёме спирта этилового 96% (ч.д.а.) при 65±2°С, затем растворитель выпаривали под вакуумом до постоянной массы. Использовали вакуумный насос и водяную баню, температура 40±2°С. Растворение образцов изучали, используя магнитную мешалку с подогревом и устройством термостатирования. Концентрацию метронидазола определяли на спектрофотометре, используя кварцевые кюветы, при длине волны 318±2 нм. Для фильтрования растворов использовали шприцевые насадки, поры – 0,45 мкм, фильтр – нейлон. Микрокристаллоскопию проводили на микроскопе с цифровой камерой. Оптические свойства растворов исследовали, используя кварцевую кювету и зеркальную камеру (экспозиция снимка 20 сек.).

**Результаты.** Получение твердых дисперсий увеличивает полноту и скорость растворения метронидазола. Растворимость метронидазола из твердых дисперсий повышается на 14–17% в сравнении с исходной субстанцией. Комплекс физико-химических методов анализа, включающий: УФ-спектрофотометрию, микрокристаллоскопию и изучение оптические свойства полученных растворов, позволяет утверждать, что повышение растворимости метронидазола из твердых дисперсий объясняется потерей кристалличности и образованием твёрдого раствора действующего вещества и солюбилизирующим действием полимера с образованием коллоидных растворов метронидазола при последующем растворении твердой дисперсии в воде.

**Заключение.** Получение твердых дисперсий с полиэтиленгликолями улучшает растворение метронидазола в воде. Полученные результаты планируется использовать при разработке быстрорастворимых твёрдых лекарственных форм метронидазола с ускоренным высвобождением и повышенной биодоступностью.

**Ключевые слова:** твёрдая дисперсия; растворимость; метронидазол; полиэтиленгликоль

**Список сокращений:** ТД – твёрдая дисперсия; ПЭГ – полиэтиленгликоль; НИР – научно-исследовательская работа

## INTRODUCTION

This work continues the promising scientific area of “solid dispersions in medicine and pharmacy”.

At the moment, the study of solid dispersions (SDs) is being carried out at I.M. Sechenov First Moscow State Medical University on the basis of the departments of the Institute of Pharmacy n. a. A.P. Nelyubin: “pharmaceutical technology” and “analytical, physical and colloidal chemistry”. The work is carried out within the framework of research & development (R&D): “Increasing the bioavailability of drugs using solid dispersions.” The expected social-and-economic effect of R&D is the production of innovative drugs with an increased bioavailability at minimal economic costs, as well as an active import substitution.

Within the framework of this scientific area, solid

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-3-195-204

dispersions of more than 30 poorly soluble medicinal substances from different pharmacological groups were obtained and studied over the past 20 years on the basis of the First Moscow State Medical University n. a. I.M. Sechenov. These medicinal substances are: albendazole, amoxicillin trihydrate, ampicillin trihydrate, anestezin, acetomepregenol, acyclovir, benzonal, diclofenac (the acid form), indomethacinic acid, quverethacin, methyluracil, naftifine hydrochloride, nifidepine, nozepam, parmidin, prothionamide, riboflavin, rifampicin, rutin, synthomycin, streptocid, sulfadimethoxin, phenazepam, furazolidone, furacilin, erythromycin, etc. [1–10].

Metronidazole is an antimicrobial and antiprotozoal drug that has been successfully used in therapy for over 60 years for the treatment of infectious diseases caused by anaerobic bacteria, as well as for the treatment of protozoal infections (amoebiasis, giardiasis, trichomoniasis) [11]. As a typical representative of the group of imidazole derivatives (1,3-diazole), metronidazole is of particular interest for this study. As an antibacterial agent, metronidazole is active against gram-negative anaerobes *Bacteroides spp.: B. fragilis, B. ovatus, B. distasonis, B. vulgatus B. thetaiotaomicron); Fusobacterium spp*. and a number of gram-positive anaerobes (*Eubacterium spp*.; *Peptococcus niger; Clostridium spp.; Peptostreptococcus spp.* The minimum inhibitory concentration for these strains is 6.250–0.125 μg/ml.

A separate area of metronidazole application is the eradication of *Helicobacter pylori* in duodenal ulcer and/or stomach ulcer. Metronidazole is used in triple therapy: bismuth-based drugs; the drugs that block H2 receptors; the drugs that inhibit the proton pump. In cases a patient has an intolerance to clarithromycin or amoxicillin, Helicobacter pylori therapy is carried out using metronidazole as a substitute for these antibiotics (0.5 g 2–3 times a day for 7 days) [11, 12].

In dentistry, metronidazole is used for various localized infections caused by anaerobes in periodontal diseases and maxillofacial inflammations. A gel, which includes a combination of chlorhexidine and metronidazole, is used in dentistry. Its indications are: infectious and inflammatory diseases of the oral mucosa and parodontium – acute and chronic – gingivitis, periodontitis, necrotising ulcerative Vincent's gingivitis, postextraction alveolitis, aphthous stomatitis. Metronidazole is used in dentistry for systemic pharmacotherapy.

In dermatology, metronidazole is used to treat rosacea [11–13]. The widespread use of metronidazole in gastroenterology, dentistry, dermatology, gynecology, etc. was the cause of the emergence of various dosage forms. Therefore, on the Russian pharmaceutical market, metronidazole is presented in the form of tablets, solutions, creams; is included in gels and suppositories along with other active ingredients. The substance of metronidazole (Fig. 1) is a crystalline powder of light yellow or white; it is slightly soluble in water, acetone and ethanol (1 : 100), which can limit its use in some cases, causes difficulties of a technological nature in the creation of new drugs, and reduces their bioavailability.

It is possible to increase the solubility and accelerate the release of substances from the dosage form by "the method of solid dispersions" (SDs) [1–10; 14–17]. SDs are either multicomponent systems that include an active substance and a carrier (a solid phase of a drug dispersed in a polymer), or solid solutions of a drug in a carrier. In some cases, the formation of complexes of various natures of the active substance with the carrier material can be observed [1, 2, 13]. Various polymeric substances are used in the role of the SD carrier [17–19].

**THE AIM** of the work is to study the effect of solid dispersions using polyethylene glycols of various molecular weights on the solubility of metronidazole in water.

## MATERIALS AND METHODS

The substance of metronidazole used in the experiment, was manufactured by Hubei Hongyuan Pharmaceutical Technology Co., Ltd. (China). It corresponds to the Product specification file (State Pharmacopoeia, Russia, XIV$^{th}$ ed., Pharmacopeial monograph.2.1.0136.18). To obtain SDs, PEGs of various molar masses – 1500, 2000, and 3000 g/mol – were used as carriers (Merck, Germany).

### Technology for preparing solid dispersions with PEG

The literature analysis and the accumulated actual experience make it possible to assert that, in case of PEG, the optimal technology for obtaining SDs is "solvent removal" [3, 5–7, 10, 20, 21–23]. The calculated amounts of metronidazole and polymer were dissolved in a minimum volume of 96% ethyl alcohol (analytical grade) by heating to 65±2°C, then the solvent was evaporated under vacuum to the constant weight. A UED-Lab 115 vacuum pump (China) and a UT-4301E water bath (Ulab, China) were used at the temperature 40±2°C [1, 2, 16, 18, 22].

### Study of metronidazole dissolution

Carried out according to the technique described in the works of Krasnyuk I.I. et al. [1] and Beliatskaya A.V. et al. [2]. The main problem was the impossibility of using the methods according to General Pharmacopoeia Monograph 1.4.2.0014.15 "Dissolution for solid dosage forms". This is associated with the preparation of saturated solutions of metronidazole under study. The SDs obtained in the work are very sticky, thick white masses or powders of soft consistency, prone to sticking together. The conditions described in GPM 1.4.2.0014.15 for studying the dissolution of these objects, are not always acceptable. In this regard, a modified technique was used during the work. Preliminary studies [6–8] prove that the dissolution test on the "rotating basket" device

presents results similar to those obtained by the modified methods.

Thus, the dissolution of the samples was studied using a heated magnetic stirrer equipped with an RCT BASIC thermostatting device (IKA, Germany). The samples for dissolution were selected in such a way that a saturated solution of metronidazole would be achieved. The temperature of the dissolution medium was 37±1°C. The samples were immersed in 150 ml of purified water; they were continuously stirred (200 rpm).

To study the dynamics of the metronidazole dissolution, the samples (5 ml) were thieved at the intervals of 5, 10, 15, 20, 30, 40, 50, 60 min. The medium was replenished up to 150 ml with purified water. The samples were filtered.

### Measurement of metronidazole concentration

In the experiment, a UNICO2800 spectrophotometer (Unitedproducts & instruments, USA) and quartz cuvettes (the absorbing layer of 10 mm) were used. If necessary, the samples were diluted with purified water, the optical density of the resulting solution was measured at the wavelength of 318±2 nm (the maximum absorption of metronidazole). The results are presented in Table 1, Fig. 2, 3.

### Filtration

The filtration was carried out using syringe nozzles with Minisart® filters (Sartorius, Germany) with a pore diameter of 0.45 μm, the filter was nylon.

### Microcrystalloscopy

A Levenhuk D50LNG microscope (PRC for Levenhuk, Inc., USA) with a digital camera was used. The study was carried out according to the methodology [1, 2, 6, 7, 9]. In case of the metronidazole substance, the powder was placed on a glass slide, mixed with a drop of vaseline oil, covered with a cover glass, and microscoped. In case of SD, a drop of the solution of metronidazole and PEG (in the proportions corresponding to SD) in 96% ethyl alcohol was applied to a glass slide, the solvent was completely removed and microscoped.

Separately, PEGs were studied in a similar way. A drop of the PEG solution was applied to a glass slide, the solvent was completely removed, and the PEG was solidified and microscoped.

The recrystallized substance of metronidazole was additionally investigated after the removal of alcohol. A drop of the metronidazole solution in 96% ethyl alcohol was placed on a glass slide, microscoped after a complete removal of the solvent. The micrographs of the studied samples with the microscopic condition are shown in Fig. 4.

### Study of the optical properties of solutions

A quartz cuvette (the layer of 50.0 mm) was used. The cuvette was filled with a filtered solution of the studied sample. An opaque partition with a hole (1 mm in the diameter) was placed between the cell wall and the light source. A thin beam of white light was directed through the hole onto the cuvette. In the darkened room, the digital images of the Faraday-Tyndall phenomenon were filmed. A Canon 5D MarkII SLR camera (the image exposure of 20 sec) was used. The results are shown in Fig. 5.

### Statistical processing

Statistical processing of the values of metronidazole concentrations in solutions was carried out in accordance with General Pharmacopoeia Monograph 1.1.0013.15 (SP RFXIV): n = 5, p = 95%.

## RESULTS AND DISCUSSION

Polyethylene glycols (PEGs) are promising carriers of solid dispersions [10]. PEGs are tasteless and odorfree, readily soluble in water and alcohol, chemically stable, biologically harmless, resistant to high temperatures during sterilization. PEGs are insensitive to fluctuations in pH and the presence of electrolytes; they are resistant to the action of microorganisms due to the presence of primary hydroxyl groups in the molecule [3, 21]. The PEG consistency depends on the molecular weight. Up to 400 g/mol, PEGs are viscous colorless liquids; with a mass of more than 400 to 1000 g/mol; they are substances with the consistency of soft wax; PEGs with a mass of 1500 g/mol and more are solid. In view of the fact that the obtained data are later planned to be used in the development of solid, rapidly dissolving dosage forms of metronidazole, PEGs of a solid consistency with weights of 1500, 2000, and 3000 g/mol were chosen as the actual objects of research. The selected polymers are often used as auxiliary substances in the production of tablets and granules [5].

The use of preparations based on SD and PEG is promising due to the bioadhesive qualities of PEGs (as high molecular weight compounds). Upon contact with mucous membranes or skin, PEG macromolecules are adsorbed and, as a rule, increase the permeability of cell membranes, promoting active transmucosal transfer of the active substance. The analysis of patent and scientific literature did not reveal information on the use of PEGs in the technology of solid dosage forms as carrier polymers for the preparation of SDs with metronidazole in order to increase its solubility in water.

Based on the analysis of the scientific literature and preliminary actual research, the range of optimal metronidazole:PEGs were determined: from 1:1 to no more than 1:5 (by weight) [1-9]. Taking into account the physicochemical properties of PEG (as an excipient) and its effect on the technological characteristics of solid dosage forms (for example, on their strength), this range of ratios is optimal for the future inclusion of metronidazole SD with PEG in the composition of solid dosage forms.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-3-195-204

**Table 1 – Changes in the concentration of metronidazole solutions and solid dispersions over time**

| № | Sample composition | Sample weight (g) | Average value of metronidazole concentration (mg/ml) in the sample solution from the dissolution beginning; n = 5 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sampling time (min.) | | | | | | | |
| | | | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| 1 | Metronidazole – substance | 3.0 | 7.767 | 7.944 | 8.221 | 8.400 | 8.734 | 8.846 | 8.950 | 9.003 |
| 2 | SD metronidazole: PEG-1500 (1:1) | 2.0:2.0 | 8.342 | 10.473 | 12.885 | 11.773 | 10.661 | 9.789 | 9.444 | 9.402 |
| 3 | SD metronidazole: PEG-1500 (1:3) | 2.0:6.0 | 8.156 | 9.267 | 9.590 | 10.083 | 10.343 | 10.602 | 10.423 | 10.244 |
| 4 | SD metronidazole: PEG-1500 (1:5) | 2.0:10.0 | 2.971 | 4.180 | 5.408 | 6.383 | 7.875 | 9.112 | 10.303 | 10.534 |
| 5 | SD metronidazole: PEG-2000 (1: 1) | 2.0:2.0 | 8.165 | 9.272 | 10.114 | 9.415 | 9.721 | 10.026 | 10.214 | 10.402 |
| 6 | SD metronidazole: PEG-2000 (1: 5) | 2.0:10.0 | 5.969 | 6.980 | 7.711 | 8.667 | 9.144 | 9.499 | 9.683 | 9.686 |
| 7 | SD metronidazole: PEG-3000 (1:1) | 2.0:2.0 | 4.757 | 6.984 | 8.156 | 8.601 | 8.717 | 8.973 | 9.457 | 9.639 |
| 8 | SD metronidazole: PEG-3000 (1:5) | 4.0:20.0 | 4.460 | 7.698 | 9.127 | 8.950 | 9.190 | 9.370 | 9.549 | 9.751 |

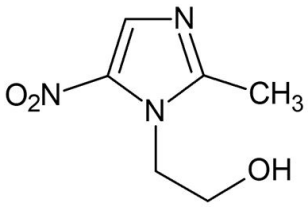


**Figure 1 – Structural formula of metronidazole $C_6H_9N_3O_3$, 2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethanol, (171.15 g/mol)**

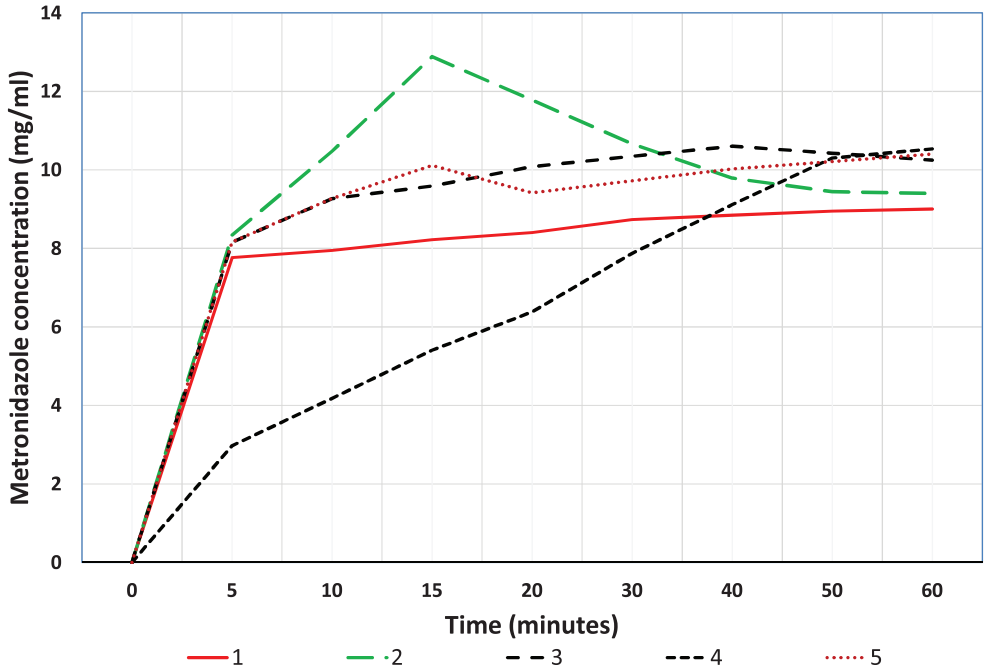


**Figure 2 – Changes in concentrations of metronidazole and SD solutions with PEG-1500 and PEG-2000 over time**

Note: 1 – metronidazole (substance); 2 – SD metronidazole : PEG-1500 (1: 1); 3 – SD metronidazole:PEG-1500 (1: 3); 4 – SD metronidazole:PEG-1500 (1: 5); 5 – SD metronidazole:PEG-2000 (1: 1).

*ISSN 2307-9266 e-ISSN 2413-2241*

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

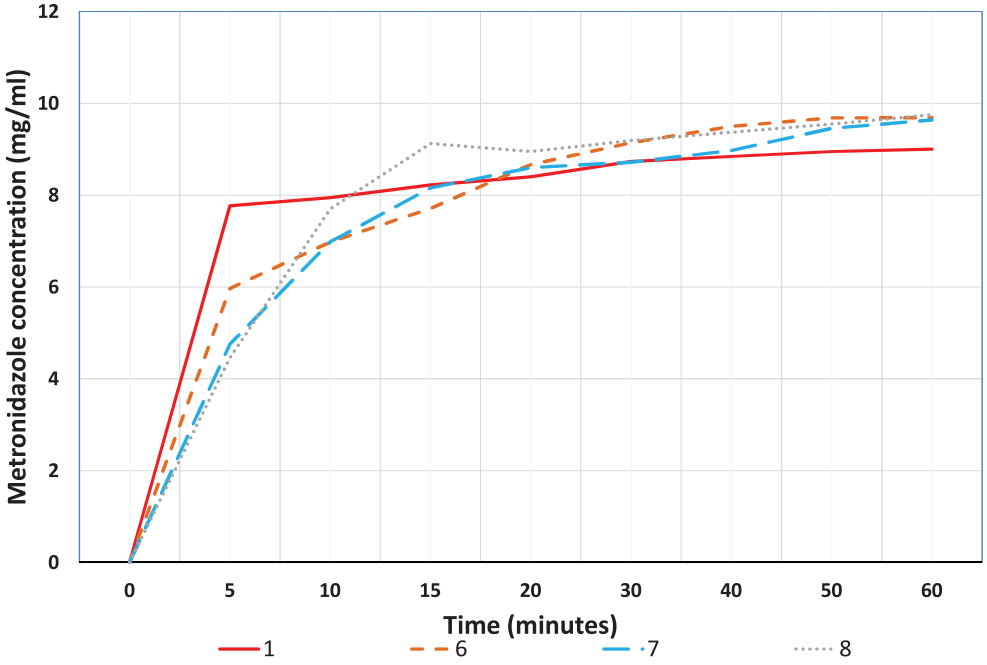


**Figure 3 – Changes in concentrations of metronidazole and SD solutions with PEG-2000 and PEG-3000 over time**

Note: 1 – metronidazole (substance); 6 – SD metronidazole: PEG-2000 (1:5); 7 – SD metronidazole: PEG-3000 (1:1); SD metronidazole: PEG-3000 (1:5)

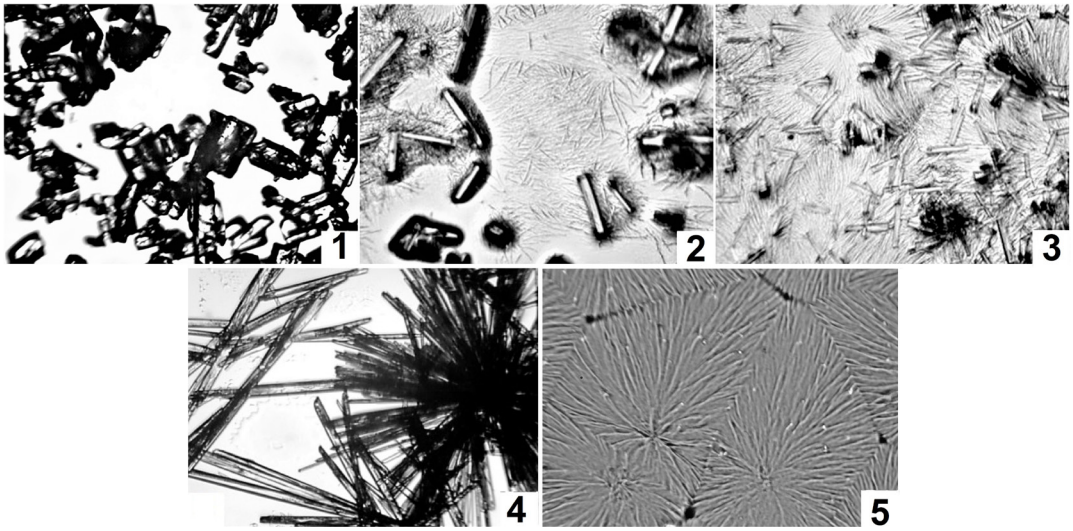


**Figure 4 – Microcrystalloscopic analysis (magnification × 64)**

Note: 1 – metronidazole (substance); 2 – SD metronidazole: PEG-1500 (1:1); 3 – SD metronidazole: PEG-1500 (1:3); 4 – recrystallized metronidazole substance; 5 – PEG-1500 after solvent removal

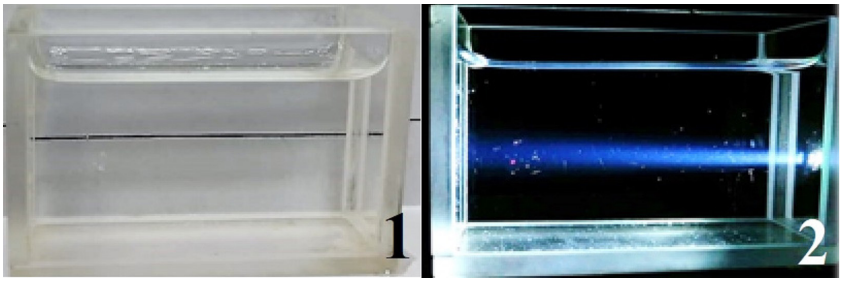


**Figure 5 – Optical properties of SD metronidazole solutions**

Note: PEG-1500 (1:1): 1 – appearance of the solution in daylight; 2 – the same solution, observation of Faraday-Tyndall cone

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-3-195-204

To study the dissolution of weighed portions of the studied samples, the SD was taken in excess with respect to the solvent (purified water). The relative error for the average concentration values is ≈4.79%. The change in the solubility was calculated as the ratio of the concentration of a saturated solution of the studied sample to the concentration of a saturated solution of the metronidazole substance 60 min after the beginning of the dissolution process. By the end of the experiment, the solutions of all studied samples were cloudy and saturated. The original substance of metronidazole dissolves rather slowly (Fig. 2). After 5 minutes from the beginning of the experiment, the concentration of metronidazole reaches 7.767 mg/ml and then slightly increases, reaching an almost constant value of ≈9 mg/ml by 30 minutes.

Based on the data obtained (Table 1; Fig. 2, 3), it can be seen that in some cases metronidazole dissolves better from SD, and its solubility depends on the selected polymer and on the mass ratio of metronidazole:PEG in SD.

When using PEG-1500, the greatest increase in the solubility of metronidazole is observed in the case of SD metronidazole: PEG-1500, obtained in the mass ratios of 1:3 and 1:5 – by 14–17%. The concentration of metronidazole in the solutions of these SDs by the end of the experiment reaches 10.244 mg/ml and 10.534 mg/ml, respectively. When using PEG-2000, the greatest effect on the dissolution of metronidazole is observed in the case of SD metronidazole: PEG-2000, obtained in the mass ratio of 1: 1. The concentration of metronidazole in the solution of this SD by the time of 60 minutes reaches 10.402 mg/ml, which is 16% higher than that of the substance solution at the same time. An increase in the content of PEG-2000 in SD does not provide any pronounced increase in the solubility of metronidazole.

Thus, for SD metronidazole PEG-2000 (1:5), the solubility of metronidazole is 9.686 mg/ml, exceeding the substance solubility by 7.6% (Fig. 3). The use of PEG-3000 to obtain SD both in the ratios of 1:1 and 1:5, similarly slightly increases the solubility of metronidazole – up to 9.639 and 9.751 mg/ml, respectively (by 7.1 and 8.3%). The use of SD does not increase the dissolution rate of metronidazole in all cases. In this case, the dissolution rate of metronidazole can both increase and decrease in the first 20–30 minutes.

For solutions of some SDs, the phenomenon of supersaturation is observed. Upon dissolution of SD metronidazole: PEG-1500 (1:1) and SD metronidazole: PEG-2000 (1:1), the concentration of metronidazole sharply increases to the maximum value during the first 15 minutes. Then, probably as a result of recrystallization, the concentration decreases, with the output of the values “on the plateau” (50-60 minutes). Thus, the greatest increase in the rate of metronidazole dissolution is observed from SD with PEG-1500 (1:1). At the moment of 15 minutes from the beginning of dissolution, the concentration of metronidazole in the solution of this SD reaches its highest value – 12.885 mg/ml, which is 57% higher than the value of the concentration in the solution of the substance at the similar point of time. However, further on, by the 40$^{th}$ min, the concentration level of metronidazole in the SD solution decreases to the value of ≈9.8 g/ml. In the authors’ opinion, the above-described fluctuations in the metronidazole concentration of the SD solutions are associated with a number of mutually opposite processes. On the one hand, these are the processes of the metronidazole release and the PEG matrix upon dissolution of SD, and its transition into an aqueous medium in a molecular colloidal form. In this case, PEG plays the functions of a solubilizer (with a low content in SD) and/or colloidal protection, stabilizing the previously achieved high level of the metronidazole concentration. On the other hand, the processes of metronidazole recrystallization, coagulation of its colloidal particles occur, and the salting-out effect of PEG may affect it. This is especially noticeable in the case of SD with a high polymer content. The balance of these processes and their result in achieving a certain level of metronidazole concentration in the solution of its SD is difficult to describe and is a topic for the SD research.

Based on the results of the microscopy (Fig. 4), the initial substance of metronidazole is particles of the substance with a clearly pronounced crystalline structure. The fragments of crystals are colorless, transparent, oblong, layered, and in most cases, they are of the same type. Regular parallel faces in the form of a rectangular parallelepiped are traced. Presumably, the powder of the substance had not previously undergone intensive micronization. Recrystallized metronidazole differs from the initial substance and has the form of pronounced needle-like, transparent crystals. The edges are even, sometimes collected in stellate clusters. Polymer carrier (PEG) is a colorless, transparent mass located on the surface of a slide with a film without an internal structure. The surface is folded. With a high degree of probability, it can be argued that this is a non-crystalline, amorphous structure. SD with PEG are heterogeneous systems consisting of at least 3-4 phases. Some structures have a partially needle-like architecture- probably, a recrystallized substance. Very small (presumably amorphous), difficult to identify objects were notified. They represent either a stopped initial stage of recrystallization of the substance in a viscous polymer, or (possibly) its polymorphic modification, or a product of complexation with PEG. Considering the fact that the content of metronidazole in SD is from 30 to 50% by weight, the transparent background is most likely to be a solid solution of metronidazole in PEG.

Thus, SD metronidazole: PEG is a complex microcrystalline pattern that combines the features of the initial substance of metronidazole (crystalline and amorphous in nature), PEG, their solid solution, and, possibly, complexation products. When studying SD, thermo-methods are very common. With regard to SD, they are based

on the fact that melting or the thermal destruction of the active substance molecule incorporated into the polymer matrix, occurs during or after the thermal destruction of the carrier polymer. The main criterion for the formation of the complex is the disappearance of the thermal effects typical of the active substance, as an individual phase. In this case, when examining SD of metronidazole, the use of, for example, differential scanning calorimetry may be of an auxiliary nature. However, the information obtained by microscopy, in the authors' opinion, is quite sufficient to make an assumption about the effect of the crystallinity of metronidazole in SD on the increase in the solubility of the active substance from the PEG polymer matrix.

In a number of works devoted to the preparation and study of SDs, the method of IR spectroscopy is often used. Based on the analysis of the characteristic bands shift of the active substance in SD, it suggests the formation of hydrogen bonds in the complex between the carrier and drug molecules. The preceding investigation of the authors' suggest that this research method is not always possible to use when studying such multicomponent systems as SD [1–10]. First of all, this is due to the pronounced shielding effect of polymers (in this case, PEG), due to which it is often impossible to obtain a true picture of the SD components interaction. The IR spectrum of SD with PEG is almost completely identical to the IR spectrum of the studied polymer and contains almost no characteristic bands of the active substance itself. However, in the absolute majority of cases, even if the interaction with PEG was observed, it was not of a covalent nature; it was a weak interaction at the level of the occurrence of hydrogen bonds. The absence of any interaction between the components of the studied SD is indirectly confirmed by UV spectroscopy of the studied samples.

The UV spectrum of metronidazole in SD with PEG is completely identical to the UV spectrum of the initial substance of metronidazole. Microcrystalloscopy makes it possible to conclude that one of the reasons for the increase in the solubility of metronidazole from SD with PEG, is the loss of its crystalline structure even before the SD dissolution in water. At the stage of the SD preparation, when the common solvent is removed under vacuum, metronidazole is partially dissolved in the SD matrix in the medium of the PEG carrier, to form a solid solution. Then, when dissolved in water, SD, as the polymer dissolves, releases the active ingredient in a molecular colloidal form. In this case, PEG, possibly, additionally has a solubilizing effect, stabilizing the concentration of metronidazole. In addition, according to a number of reference materials [17, 19, 20, 23–25], the formation of their colloidal solutions is an important factor contributing to an increase in the dissolution of active substances from SD.

In this regard, the optical properties of the solutions obtained in the work, were studied. For the filtered solutions of all the SDs studied in the work with PEG, the Faraday-Tyndall cone is observed – scattering of light of a bluish tint due to the colloidal-dispersed state of the dissolved metronidazole (Fig. 5).

Herewith, the solutions of the auxiliary substances (PEGs) and the saturated solutions of the metronidazole substance or its mixtures with the studied polymers, similarly prepared for the study, did not demonstrate the Faraday-Tyndall effect. The results obtained, underline the fundamental importance of obtaining SD by the method of "the solvent removal" described in this work, for increasing the solubility of metronidazole in water.

## CONCLUSION

The analysis of the data obtained indicates that the improvement in the dissolution of metronidazole from SD, carried out by the method of "the solvent removal" with the use of 96% ethyl alcohol as a common solvent, is associated with a decrease in the crystallinity of metronidazole upon receipt of its SD and solubilization, as well as with the formation of metronidazole colloidal solutions stabilized with PEG when SDs are dissolved.

The optimal PEG for the SD production is PEG with a molecular weight of no more than 1500 g/mol, and the best ratio of SD components (metronidazole: PEG) is 1:1 by weight. The results obtained will be used in the development of the technology of "effervescent" tablets and granules of metronidazole containing its SD with PEG.

## FUNDING

The work was carried out without attracting external sources of funding.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHORS' CONTRIBUTION

Ivan I. Krasnyuk (Jr.) – general management and planning of the experiment; Savva R. Naryshkin and Ivan S. Bobrov – study of metronidazole dissolution; Ivan I. Krasnyuk– measuring metronidazole concentrations of solutions; Anastasia V. Belyatskaya – preparation of solid dispersions; Olga I. Stepanova– collecting and processing of literature data; Aleksandr N. Vorobiev – investigation of solutions optical properties; Victoria G. Yankova – analysis, processing and preparation of graphic materials; Julietta V. Rau – microcrystalloscopic examinations. All the authors participated in the discussion of the results and writing the article.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-3-195-204

## REFERENCES


1. Krasnyuk II, Beliatskaya AV, Krasnyuk II, *et al.* Influence of Polymers on the Physicochemical Properties of Benzonal in Solid Dispersions. *Moscow Univ. Chem. Bull.* 2020; 75: 388–90. DOI: 10.3103/S0027131420060127.
2. Beliatskaya AV, Krasnyuk II, Elagina AO, et al. Study of the Solubility of Furazolidone from Solid Dispersions with Polyvinylpyrrolidone. Moscow Univ. Chem. Bull. 2020; 75: 43–6. DOI: 10.3103/S0027131420010046.
3. Kosenkova SI, Krasnyuk II, Krasnyuk Jr II, et al. Antimycotic Activity of Naftifine Hydrochloride Solution in Combination with Poly(Ethylene Glycols). Pharm Chem J. 2020; 54: 310–1. DOI: 10.1007/s11094-020-02196-w
4. Belyatskaya AV, Kashlikova IM, Krasnyuk II, Krasnyuk II Jr, Stepanova OI, Vorob'ev AN. Development of compositions and production technology for gels with a solid dispersal of nitrofural. Pharmaceutical Chemistry Journal. 2020; 53(10): 981–5. DOI: 10.1007/s11094-020-02109-x.
5. Krasnyuk II Jr, Ovsyannikova LV, Stepanova OI, Belyatskaya AV, Krasnyuk II, Grikh VV, Kosheleva TM, Kozin DA, Skovpen YV. Development of dosage forms containing solid dispersion of diclofenac. Pharmaceutical Chemistry Journal. 2018; 52(4): 357–60. DOI: 10.1007/s11094-018-1821-6.
6. Krasnyuk II Jr, Beliatskaya AV, Krasnyuk II, Stepanova OI, Korol LA, Valeeva AM, Grikh VV, Ovsyannikova LV, Kosheleva TM. Effect of solid dispersions on the dissolution of ampicillin. BioNanoScience. 2017;7(2): 340–4. DOI: 10.1007/s12668-016-0342-6.
7. Krasnyuk II Jr, Kosheleva TM, Belyatskaya AV, Krasnyuk II, Stepanova OI, Skovpen YV, Grikh VV, Ovsyannikova LV. Effect of solid dispersions with polyethylene glycol 1500 on the solubility of indomethacin. Pharmaceutical Chemistry Journal. 2018;52(3):241–4. DOI: 10.1007/s11094-018-1799-0.
8. Belyatskaya AV, Krasnyuk II Jr, Krasnyuk II, Stepanova OI, Kosheleva TM, Kudinova TP, Vorob'ev AN, Maryanyan MM. Dissolution of ketoprofen from poly(ethylene glycol) solid dispersions. Pharmaceutical Chemistry Journal. 2019; 52(12):1001–6. DOI: 10.1007/s11094-019-01941-0.
9. Belyatskaya AV, Krasnyuk II Jr, Krasnyuk II, Stepanova OI, Abgaryan ZA, Kudinova TP, Vorob'yov AN, Nesterenko IS. Study on the solubility of ketoprofen from solid dispersions with polyvinylpyrrolidone. Moscow university chemistry bulletin. 2019;74(2):93–9. DOI: 10.3103/S0027131419020056.
10. Silaeva SYu, Belenova AS, Slivkin AI, Chupandina EE, Naryshkin SR, Krasnyuk II Jr, Krasnyuk II. Use of solid dispersion systems in pharmacy. Condensed Matter and Interphases. 2020;22(2):173–81. DOI: 10.17308/kcmf.2020.22/2820.
11. Troyanova SYu, Korsunskaia IM, Sorkina IL, Sobolev VV. Justification of the efficacy of metronidazole in the treatment of rosacea. Klinicheskaya Dermatologiya i Venerologiya. 2017;16(5):45–8. DOI: 10.17116/klinderma201716545-48. Russian
12. Feres M, Retamal-Valdes B, Mestnik MJ, de Figueiredo LC, Faveri M, Duarte PM, Fritoli A, Faustino E, Souto MLS, de Franco Rodrigues M, Giudicissi M, Nogueira BCL, Saraiva L, Romito GA, Pannuti CM. The ideal time of systemic metronidazole and amoxicillin administration in the treatment of severe periodontitis: study protocol for a randomized controlled trial. Trials. 2018 Mar 27;19(1):201. DOI: 10.1186/s13063-018-2540-8.
13. Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. F1000Res. 2018 Dec 3;7:F1000 Faculty Rev-1885. DOI: 10.12688/f1000research.16537.1.
14. Singh N, Sarangi Mk, Solid Dispersion – a Novel Approach for Enhancement of Bioavailability of Poorly Soluble Drugs in Oral Drug Delivery System. Global Journal of Pharmacy & Pharmaceutical Sciences. 2017;3(2):30–7. DOI: 10.19080/GJPPS.2017.03.555608
15. Huang S, Mao C, Williams RO 3rd, Yang CY. Solubility Advantage (and Disadvantage) of Pharmaceutical Amorphous Solid Dispersions. J Pharm Sci. 2016 Dec;105(12):3549–3561. DOI: 10.1016/j.xphs.2016.08.017.
16. Huang Y, Dai WG. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharmaceutica Sinica B. 2013; 4(1): 18-25. DOI: 10.1016/j.apsb.2013.11.001.
17. Chen X, Partheniadis I, Nikolakakis I, Al-Obaidi H. Solubility Improvement of Progesterone from Solid Dispersions Prepared by Solvent Evaporation and Co-milling. Polymers (Basel). 2020 Apr 7;12(4):854. DOI: 10.3390/polym12040854.
18. Teodorescu M, Bercea M, Morariu S. Biomaterials of PVA and PVP in medical and pharmaceutical applications: Perspectives and challenges. Biotechnol Adv. 2019 Jan-Feb;37(1):109–31. DOI: 10.1016/j.biotechadv.2018.11.008.
19. Hou HH, Rajesh A, Pandya KM, Lubach JW, Muliadi A, Yost E, Jia W, Nagapudi K. Impact of Method of Preparation of Amorphous Solid Dispersions on Mechanical Properties: Comparison of Coprecipitation and Spray Drying. J Pharm Sci. 2019 Feb;108(2):870–9. DOI: 10.1016/j.xphs.2018.09.008.
20. Parker AS, Gilpin CJ, Stewart AA, Beaudoin SP, Taylor LS. Dissolution of indomethacin crystals into a polymer melt: role of diffusion and fragmentation. Crystal growth and design. 2019; 19(6): 3315–28. DOI: 0000-0001-6986–8252.
21. Siepmann J, Faham A, Clas SD, Boyd BJ, Jannin V, Bernkop-Schnürch A, Zhao H, Lecommandoux S, Evans JC, Allen C, Merkel OM, Costabile G, Alexander MR, Wildman RD, Roberts CJ, Leroux JC. Lipids and polymers in pharmaceutical technology: Lifelong companions. Int J Pharm. 2019 Mar 10;558:128–42. DOI: 10.1016/j.ijpharm.2018.12.080.
22. Younis MA. Solid dispersion technology, a contemporary overview on a well established technique. Universal Journal of Pharmaceutical Research. 2017; 2(3):15–9. DOI: 10.22270/ujpr.v2i3.RW1.
23. Luebbert C, Klanke C, Sadowski G. Investigating phase separation in amorphous solid dispersions via Raman mapping. Int J Pharm. 2018 Jan 15;535(1–2):245–52. DOI: 10.1016/j.ijpharm.2017.11.014.
24. Okada K, Hirai D, Hayashi Y, Kumada S, Kosugi A, Onuki Y. A Novel Approach to Evaluate Amorphous-to-Crystalline Transformation of Active Pharmaceutical Ingredients in Solid Dispersion Using Time-Domain NMR. Chem Pharm Bull (Tokyo). 2019;67(3):265-70. DOI: 10.1248/cpb.c18-00887.
25. Singh A., Van den Mooter G. Spray drying formulation of amorphous solid dispersions. Adv Drug Deliv Rev. 2016 May 1;100:27–50. DOI: 10.1016/j.addr.2015.12.010.

## AUTHORS

**Ivan I. Krasnyuk (Jr.)** – Doctor of Sciences (Pharmacy), Professor, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Analytical, Physical and Colloidal Chemistry, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0001-8557-8829. E-mail: krasnyuk.79@mail.ru

**Savva R. Naryshkin –** post-graduate student, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Analytical, Physical and Colloidal Chemistry, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0003-1775-4805. E-mail: savva.naryshkin@gmail.com

**Ivan I. Krasnyuk –** Doctor of Sciences (Pharmacy), Professor, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Pharmaceutical Technology, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0002-7242-2988. E-mail: krasnyuki@mail.ru

**Anastasia V. Belyatskaya –** Candidate of Sciences (Pharmacy), Associate Professor, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Pharmaceutical Technology, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0002-8214-4483. E-mail: av.beliatskaya@mail.ru

**Olga I. Stepanova –** Candidate of Sciences (Pharmacy), Senior Lecturer, Department of Pharmacology, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Pharmacology, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0002-9885-3727. E-mail: o.i.nikulina@mail.ru

**Ivan S. Bobrov –** student, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Analytical, Physical and Colloidal Chemistry, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0001-8263-5541. E-mail: bobrov2602@yandex.ru

**Viktoria G. Yankova –** Candidate of Sciences (Pharmacy), Associate Professor, Institute of Pharmacy n. a. A.P. Nelyubin, Department of Analytical, Physical and Colloidal Chemistry, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University). ORCID ID: 0000-0002-8233-5087. E-mail: yankowa@rambler.ru

**Julietta V. Rau** – Candidate of Sciences (Chemistry), Associate Professor of the Department of Analytical, Physical and Colloidal Chemistry, First Moscow State Medical University n. a. I.M. Sechenov (Sechenov University), Institute of Pharmacy n. a. A.P. Nelyubin; Istituto di Struttura della Materia, Consiglio Nazionale delle Ricerche (ISM-CNR), Via del Fosso del Cavaliere, 100-00133 Rome, Italy. ORCID ID: 0000-0002-7953-1853. E-mail: giulietta.rau@ism.cnr.it

**Alexander N. Vorobiev –** Candidate of Sciences (Pharmacy), Head of the Laboratory of Industrial Pharmaceutical Technology, Center for Collective Use (REC), Peoples' Friendship University of Russia. ORCID ID: 0000-0002-7182-9911. E-mail: alek_san2007@mail.ru